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Abstract: In patients with normal SPECT MPI, a CAC >1000 confers a high diagnostic added value for detecting CAD. This is not solely based on unmasking balanced ischaemia due to epicardial 3-VD, as it occurred predominantly in patients with 1-VD and 2-VD.

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# **Very high coronary calcium score unmasks obstructive coronary artery disease in patients with normal SPECT MPI**

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Running title: Extensive CAC unmasks CAD in normal SPECT

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## Abstract

**Objectives:** To study the clinical impact of a very high coronary artery calcium score (CAC >1000) in patients with no known coronary artery disease (CAD) and normal single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI). The secondary aim was to evaluate whether triple vessel disease would support the notion of balanced ischemia as an underlying mechanism of false negative SPECT MPI in patients with very high CAC.

**Background:** No clinical data exists on the clinical value of extensive CAC in patients with normal SPECT MPI.

**Methods:** 50 patients with suspected CAD and normal stress/rest SPECT MPI and CAC >1000 prospectively underwent invasive coronary angiography as standard of reference. Coronary lesions with  $\geq 50\%$  luminal diameter narrowing on invasive coronary angiography were considered as significant stenosis.

**Results:** The median total CAC was 1975 (range 1018-8046). In 37/50 (74%) patients coronary angiography revealed 1-vessel disease (VD) (n = 15), 2-VD (n = 10) or 3-VD (n = 12). Twenty-six revascularizations (percutaneous coronary intervention/ coronary artery bypass grafting) were performed in 7 (6/1), 7 (6/1) and 12 (7/5) patients with 1-VD, 2-VD and 3-VD, respectively.

**Conclusions:** In patients with normal SPECT MPI a CAC >1000 confers a high diagnostic added value for detecting CAD. This is not solely based on unmasking balanced ischemia due to epicardial 3-VD as it occurred predominately in patients with 1-VD and 2-VD.

**Key Words:** Coronary artery disease, Coronary calcium score, balanced ischemia, normal SPECT/MPI

**Word count: 225**

## **Abbreviations**

CAD = coronary artery disease

CAC = coronary artery calcium score

CT = computed tomography

ECG = electrocardiogram

LVEF = left ventricular ejection fraction

MPI = myocardial perfusion imaging

PET= positron emission tomography

SPECT = single photon emission computed tomography

SSS = summed stress score

TID = transient ischemic dilation

VD = vessel disease

## Introduction

Nuclear myocardial perfusion imaging (MPI) with single photon emission computed tomography (SPECT) is a well-established non-invasive method for detecting ischemia and the prognostic evaluation of patients with known or suspected coronary artery disease (CAD). A large body of literature has provided good evidence that normal SPECT MPI scan has a very high negative predictive value for ischemic heart disease and cardiovascular events in a general population. Atherosclerosis as an early stage of coronary heart disease is frequently associated with coronary calcifications.<sup>1-4</sup> Recently, the coronary calcium (CAC) score has emerged as a new technique with incremental prognostic value compared to conventional cardiovascular risk factors. High values of CAC are often an indicator of stenotic lesions and are associated with an increased risk of cardiovascular events.<sup>5-8</sup> Because of the large discrepancy between the anatomic extent of CAD and ischemia - since many stenoses do not result in abnormal perfusion - the combination of the morphological anatomic information from CAC with functional information obtained from MPI may provide complementary information for the clinician.<sup>9-13</sup> Due to the widespread availability of multislice computed tomography (CT) scanners and particularly with the integration of the latter into hybrid SPECT/CT or positron emission tomography (PET)/CT devices where low dose non-contrast CT scan for attenuation correction can be used for calculating CAC the clinical experience with CAC is growing.<sup>8, 14</sup> However, in a small but important subset of patients results from the two modalities have been conflicting, i.e. normal SPECT MPI despite very high CAC.<sup>15-17</sup> In a recent pilot study a cut off value for CAC at 709 was identified for the prediction of angiographic CAD despite normal SPECT MPI findings, suggesting balanced ischemia in multivessel disease.<sup>8</sup> Although these data support the notion

that CAC may offer incremental diagnostic information over SPECT data for identifying patients with significant CAD and negative MPI results, systematic data is lacking.

Therefore, the aim of the present study was to prospectively identify the rate of obstructive CAD in patients with normal SPECT MPI and a CAC >1000. This cut off value was chosen as previously suggested<sup>16, 18</sup> - although slightly higher than the value described above<sup>8</sup> - in order to ensure a high specificity in detection of clinically relevant CAD in agreement with the position statement of the working group on Nuclear Cardiology and Cardiac CT of the European Society of Cardiology classifying a CAC >1000 as extensive.<sup>19</sup> A secondary aim was to evaluate whether 3-vessel disease (VD) would support the notion of balanced ischemia as an underlying mechanism of false negative SPECT MPI in the presence of CAC >1000.

## Methods

### Study population

The present study included 50 consecutive patients with a suspected but no known CAD normal gated-SPECT and a CAC >1000. A gated-SPECT result was considered as normal as follows: no visual perfusion defect, summed stress score (SSS) <3, a left ventricular ejection fraction (LVEF) at rest (female/male) >50/45%<sup>20</sup> and regular heart rate. An invasive coronary angiography served as a standard of reference and was performed based on previous data indicating in patients with normal SPECT MPI and high CAC a high incidence of angiographic CAD<sup>8</sup> and an adverse outcome.<sup>16-17</sup>

Despite lack of ischemia in SPECT a further diagnostic evaluation is also supported by studies reporting that high CAC is associated with extremely elevated risk of cardiac hard events. Written informed consent was obtained from all patients.

### Gated SPECT myocardial perfusion imaging

Gated SPECT data acquisition was performed on a dual-head detector camera (Infinia or Ventri, GE Healthcare, Milwaukee, WI, USA), with a 1-day pharmacologic stress/rest MPI protocol using a weight-adjusted dose of 300 to 400 MBq of <sup>99m</sup>Tc-tetrofosmin for stress (adenosine at standard rate of 0.14 mg/kg/min over 6 minutes) and a 3 fold higher dose of <sup>99m</sup>Tc-tetrofosmin for rest image acquisition. SPECT data was analyzed by two experienced imaging cardiologists with regard to the presence of reversible and/or fixed perfusion defects on short-axis, horizontal and vertical long-axis slices as well as on the polar maps with a commercially available quantitative gated and perfusion SPECT software package (Cedars QGS/QPS; Cedars-Sinai Medical Center) which also allowed assessment of LVEF. In addition MPIs were assessed semi-quantitatively by segmental visual interpretation. A scan was



considered as normal if the summed stress score was  $<3$ .<sup>21-22</sup> The use of low isotope dose in the first part of the one day protocol precludes meaningful assessment of transient ischemic dilatation (TID). As no values of transient ischemic dilatation (TID) have been validated for low-dose ECG-gated acquisition 60 minutes after vasodilator stress, we only provided visual assessment of TID using a 0-3 visual score (0=none, 1=equivocal, 2=definite but moderate, and 3=severe), with  $\geq 2$  being considered abnormal, as previously reported.<sup>23</sup>

### **Coronary artery calcium score**

A low-dose, unenhanced CT for SPECT MPI attenuation correction was performed on a LightSpeed VCT XT 64-slice CT standalone scanner (GE Healthcare) with the following scanning parameters: prospective ECG-triggering, 2.5 mm slice thickness, 120 kV tube voltage, 200 mAs per rotation tube current, and a large scan field-of-view of 50 x 50 cm. Co-registration was accomplished by visual quality control of emission (SPECT) and transmission scans (CT) using a commercially available and well established tool intergraded in the QGS/QPS software as previously reported.<sup>24</sup>

No beta blocker was administered, and the average heart rate during acquisition was  $62 \pm 5$  bpm. From this scan Agatston scores were computed with commercially available software (Smartscore, GE Healthcare), as previously reported.<sup>24</sup>

### **Coronary angiography**

Invasive coronary angiography through the femoral artery was performed on an Allura 9 and an Allura XPER FD 10/10 (Philips Medical Systems) catheterisation equipment in an experienced catheterisation laboratory of a teaching hospital (University Hospital Zurich) following a protocol, which consists of a biplane angiography of left coronary artery with two radiation exposures in four orientations

and of the right coronary artery with two exposures in two orientations, as is routinely performed in our cardiology department as previously reported.<sup>25</sup> Additional views could be performed at the operator's discretion if necessary.

At angiography, coronary artery lesions were considered to be significant stenoses when there was  $\geq 50\%$  luminal diameter narrowing (figure 1). CAD was defined as the presence of at least one significant stenosis. Patients with left main stenosis were categorized as 2-VD.

The decision of the operator to perform percutaneous coronary intervention (PCI) or recommend coronary artery bypass graft (CABG) surgery was prospectively recorded. Lesions severity in coronary angiograms was visually assessed by two experienced interventional cardiologists and in case of disagreement a consensus between both was reached. The operators based this decision on their clinical judgment integrating the visual angiography finding with all available clinical information. No further complementary functional parameters such as for example the recently promoted functional flow reserve<sup>26</sup> were available.

### **Radiation Dose**

Values for effective radiation dose of low dose CT were calculated by multiplying the dose length product (DLP) with a conversion factor ( $k = 0.014 \text{ mSv/mGy} \times \text{cm}$ ) as previously described<sup>27</sup> and adopted in large trials.<sup>28</sup> For estimating the effective radiation dose from SPECT MPI, we used a conversion factor of  $6.9 \times 10^{-3} \text{ mSv/MBq}$ .<sup>29</sup>

### **Statistical analysis**

Quantitative intergroup comparisons were performed with the Wilcoxon test (two groups) or the Kruskal–Wallis test (more than two groups). Variables were expressed as mean $\pm$ standard deviation or median and range and categorical variables as

frequencies and percentages. CAC distribution between the main epicardial vessels was compared with the Friedman test. A p-value of  $<0.05$  was considered to be statistically significant. SPSS software (version 15.0, SPSS Inc.; Chicago Illinois) was used for statistical testing.

## Results

### Study population

The mean age of the study population was  $67\pm 9$  years, 72% were male. The mean number of risk factors was  $2.5\pm 1.2$  and most patients were classified as intermediate risk by Framingham risk score which averaged  $15.7\pm 7.3$  (median 15.5, range 3-31).

The characteristics of the study population are given in table 1.

### SPECT

According to the inclusion criteria following the study design all MPI at stress and rest were normal. The mean values for the summed rest, stress, and difference scores were  $0.3\pm 0.4$ ,  $0.7\pm 0.9$ ,  $0.5\pm 0.5$ . Mean LVEF was  $63.7\pm 4.3\%$  at rest, and  $62.8\pm 6.3\%$  after Adenosine-stress ( $p=n.s.$ ). There was no significant adenosine-induced ST segment depression. TID score was 0 in 49 patients and equivocal in 1 patient.

### Coronary angiography

Thirty-seven (74%) of the 50 patients had a significant CAD. This included 15 patients with 1-VD (30%), 10 patients with 2-VD (20%) and 12 patients with 3-VD (24%) (figure 2A). Thus, in the majority of patients (78%) with unmasked CAD the underlying disease was not 3-VD (figure 2B). Twenty-six of the 37 CAD patients (70%) underwent coronary revascularization, i.e. PCI ( $n = 19$ ) or CABG ( $n = 7$ ). Among 37 patients with CAD 28 patients revealed a stenosis  $\geq 80\%$ . While PCI was evenly distributed among 1-VD, 2-VD and 3-VD patients, CABG was predominately performed in those with 3-VD (table 2). Remarkably, in 6 of the 13 patients without angiographic CAD the absence of any luminal irregularities was reported from angiography, despite massive calcification.

### **Coronary artery calcium score**

The median CAC of the study population was 1975 (range 1018-8046), while the respective values for patients with and without CAD was 1930 (range 1026-8046) and 1977 (range 1018–3007). The median CAC in patients with 1-VD was 1476 (range 1026-5009) and tended to be higher in 2-VD and 3-VD, i.e. 2289 (range 1294–8046) and 2190 (range 1332–5915) although the difference fell short of statistical significance ( $p = 0.15$ ) (figure 2). Median CAC was significantly lower in LMA (52, range 0–751) and RCA (279, range 0-2884) compared to LAD (686, range 0–751) ( $p \leq 0.001$ ).

### **Radiation dose from SPECT MPI and Coronary artery calcium score**

The average DLP for CAC measurement was  $72.2 \pm 22.2$  mGy x cm resulting in a dose estimation of  $1.0 \pm 0.3$  mSv. Estimated effective dose from SPECT MPI was  $8.5 \pm 1.2$  mSv.<sup>29</sup>

## Discussion

The present data indicate that a CAC >1000 is a predictor of CAD in patients with intermediate pretest probability for CAD and normal SPECT MPI as angiographically significant lesions were found in 74% of the study population. The presence of atherosclerosis does not necessarily reflect obstructive coronary lesions and conversely coronary lesions do not necessarily confer hemodynamic relevance. However, an increasing CAC is generally associated with an increase in abnormal SPECT findings.<sup>10, 12-13</sup> For example, Anand et al. observed a prevalence of silent ischemia in 18% of patients with a CAC of 100-400, while the prevalence increased to 45% in patients with CAC >400.<sup>30</sup> It has been reported that a high CAC in patients with normal SPECT MPI reflects non obstructive atherosclerosis which should be recognized as a preclinical state with strong predictive value for the development of CAD<sup>5</sup> and should therefore, encourage aggressive risk factor modification according to NCEP guidelines.<sup>31</sup>

Our study extends these observations towards the upper end of the CAC spectrum. In patients with massive coronary calcifications these not only reflect an increased cardiovascular risk<sup>5</sup>, but more importantly extensive coronary calcifications with a CAC >1000 appear to unmask obstructive CAD undetected by SPECT MPI. Although the pooled literature reports an overall sensitivity of SPECT MPI to detect multivessel disease ranging from 80%-95%<sup>32-33</sup>, only in 29% of patients with 3-VD defects are found in all three territories.<sup>34</sup> By its nature, SPECT allows only detection of relative perfusion defects. Therefore, the true extent of myocardial ischemia may be underestimated particularly in vascular territories adjacent to areas with more severe coronary stenosis.

Consequently, in cases with evenly distributed ischemia without inducible flow heterogeneity among the different vessel territories balanced ischemia has been hypothesized to explain lack of perfusion defects. This however, is unlikely to be a main contributing factor to the results of the present study because a 3-VD was found in less than a third of the CAD patients. The concept of balanced ischemia may not be solely based on balanced epicardial coronary lesion severity, but rather could also be caused by microcirculatory dysfunction<sup>35-36</sup> where global hyperemic myocardial flow response and myocardial flow reserve are blunted.<sup>31</sup> A massive increase in CAC would then - although measured in the epicardial vessel - reflect involvement of the coronary microcirculatory tree, potentially associated with a decrease in myocardial flow reserve favoring a balanced hyperemic response due to blunted flow heterogeneity. This is in line with a recent study documenting that a high CAC is paralleled by endothelial dysfunction.<sup>37</sup> There is increasing evidence that even non-obstructive CAD with coronary calcification may impair hyperemic flow increases as determined with PET or MRI.<sup>39-41</sup> Concordantly, Pirich et al. have reported that relevant coronary calcification can be confined to one epicardial coronary vessel, while myocardial flow reserve is reduced in all vascular territories, therefore not revealing any perfusion abnormality by visual image analysis.<sup>38</sup> This was further substantiated by the fact that flow response was significantly lower in patients with CAC >100 compared to those with CAC <100, although overall no correlation between CAC and flow reserve was found. This, however, may have been due to the study design including only patients with relatively low CAC (median 142, range 0–915), where the vascular reactivity is not yet strongly affected. By contrast our study population with a median CAC of 1974 (range 1018-8046) represents a more advanced stadium of CAD and atherosclerosis in which microcirculatory involvement is very likely to be present even in myocardial segments subtended by non-stenotic

coronary arteries as previously reported.<sup>42</sup> This may provide the ground for balanced ischemia on the microcirculatory level of the coronary tree in patients with extensive coronary calcifications without 3-VD. This is further supported by a previous study reporting obstructive lesions in 12% of territories with normal SPECT MPI but massive calcifications.<sup>43</sup>

**Study limitations:** It may be perceived as a limitation of the present study, that the classification of coronary lesions as significant was not complemented by a functional assessment such as fractional flow reserve. The latter was not yet implemented into our daily routine during our study which was completed before the solid data from Tonino et al.<sup>26</sup> became available and before FFR has been adopted in the latest ESC guidelines for revascularization.<sup>44</sup> Therefore, the standard of reference was solely based on visual evaluation of luminal narrowing. This, however, reflects common daily practice in many coronary catheterization laboratories<sup>45</sup> and is in line with recent randomized trials evaluating coronary revascularization, like the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes), and SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) studies, in which lesions with diameter stenosis  $\geq 50\%$  based on visual estimation of the angiogram were generally considered for revascularization.<sup>46-48</sup>

An additional limitation may be the fact that our definition of normal MPI was mainly based on normal findings of perfusion and rest LVEF as our protocol with scanning late after adenosine stress does not allow to benefit from the incremental diagnostic<sup>49</sup> and prognostic<sup>23</sup> value of TID or stress induced wall motion abnormalities to identify CAD. However, the prevalence of CAC >1000 in normal SPECT MPI approximates 7% at our institution comparing favorably to the reported range of 9-11%.<sup>10, 16-17</sup> This underlines the validity of our method to classify a SPECT scan as normal, because



classifying scans inappropriately as normal would result in a higher incidence of CAC >1000.

Furthermore, the present study was focused on the prevalence of epicardial coronary lesions in patients with normal myocardial perfusion and the diagnostic value of extensive coronary calcification to unmask CAD. Therefore, the study was not powered and not designed to provide outcome data.

Finally, whether adjustment of the cut-off value for CAC would be appropriate in different patient populations with different pre-test likelihood must remain a matter of discussion as our data do not allow commenting on this.

**Conclusions:** In intermediate risk patients with normal MPI a CAC >1000 confers an incremental diagnostic value for detecting CAD. This is not solely based on unmasking balanced ischemia due to epicardial 3-VD as it occurred predominantly in patients with 1-VD and 2-VD. Therefore, further evaluation of CAD with invasive coronary angiography including FFR and / or initiation of aggressive optimal medical therapy should be considered in these patients.

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## **Conflict of interest**

None.

## **Patient consent**

Obtained.

## **Ethics approval**

This study was conducted with the approval of the local ethics committee of the University Hospital Zurich.

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**Figure 1:** Patient with a normal perfusion SPECT MPI on polar map (stress: upper panel; rest: lower panel) (A) and extensive calcifications in the calcium scoring scan of the left descending artery (LAD), left circumflex artery (LCX) and right coronary artery (RCA) with a total Agatston score of 1555 (B). The corresponding coronary angiography revealed multivessel disease with most severe lesions in the RCA (black arrows) and a total distal occlusion (white arrow) (C).

**Figure 2:** Distribution of patients (n = 50) with normal SPECT MPI and very high CAC >1000, stratified by the number of angiographically diseased vessels (0-, 1-, 2-, 3-VD).

**Figure 3:** Relationship between the number of diseased coronary vessels (0-, 1-, 2-, 3-VD) and calcium score (Agatston score). The circles demonstrate outliers. The Kruskal-Wallis p-value for a difference of calcium scores between the groups amounts to 0.15 (n.s.).

## TABLES

**Table 1** Baseline characteristics (n = 50)

Male	36 (72%)
Age (y)	
Mean $\pm$ SD	67 $\pm$ 9
Range	51-87
Framingham risk score	15 $\pm$ 7.3
Hypertension	42 (84%)
Dyslipidemia	24 (48%)
Diabetes	16 (32%)
Smoking	23 (46%)
Obesity (>30 kg/m <sup>2</sup> )	11 (22%)
Reasons for referral	
Typical angina	14 (28%)
Atypical chest pain	6 (12%)
New onset of LBBB	1 (2%)
Syncope	1 (2%)
Preoperative evaluation	19 (38%)
Dyspnea	5 (10%)
Positive exercise test	4 (8%)

LBBB = left bundle branch block

**Table 2** Angiographic CAD and revascularization

Angiographic CAD	Patients	PCI	CABG
0-VD	13	0	0
1-VD	15	6	1
2-VD	10	6	1
3-VD	12	7	5
total	50	19	7

CAD = coronary artery disease

VD = vessel disease

PCI = percutaneous coronary intervention

CABG = coronary artery bypass grafting

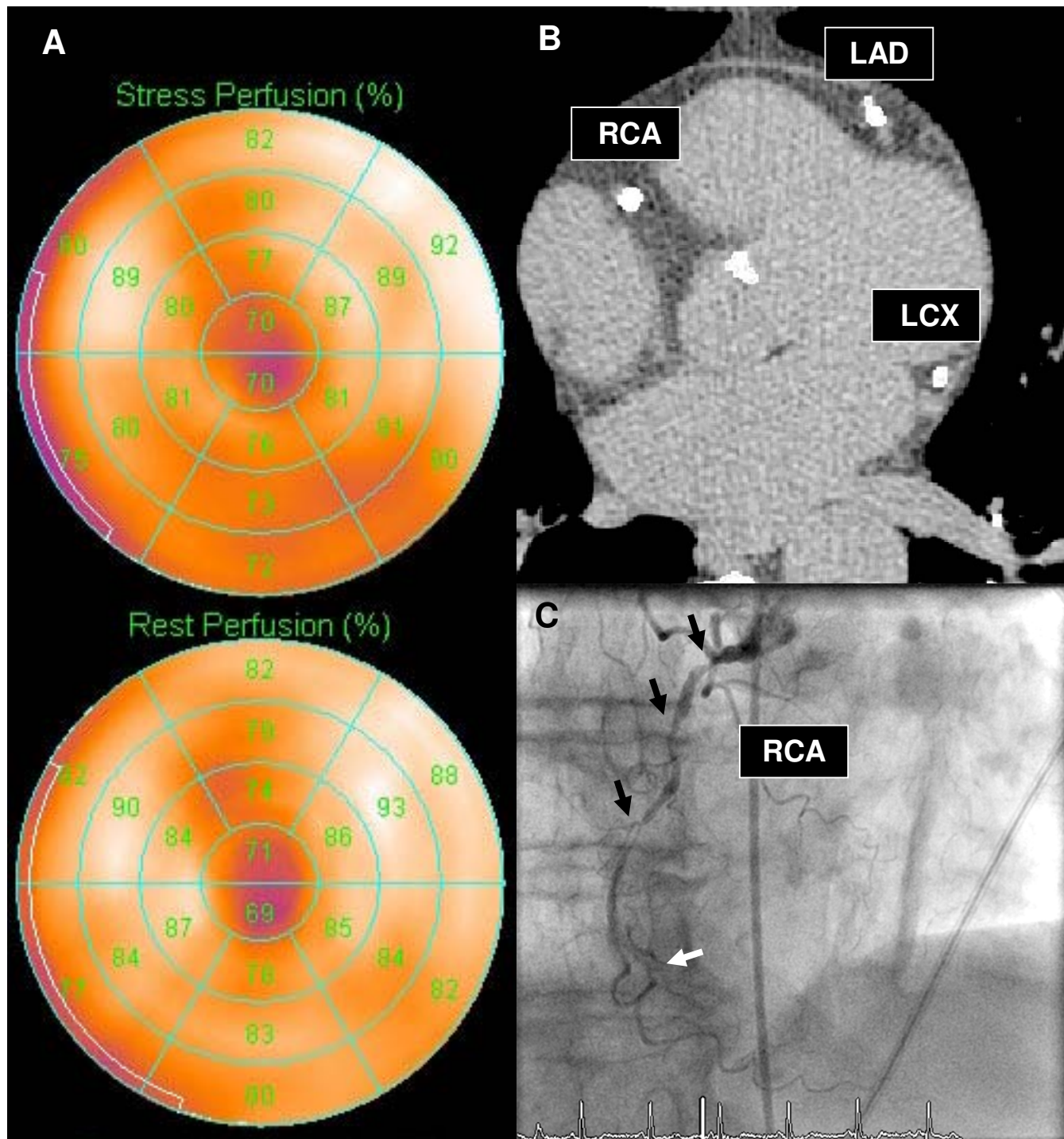


Figure 1

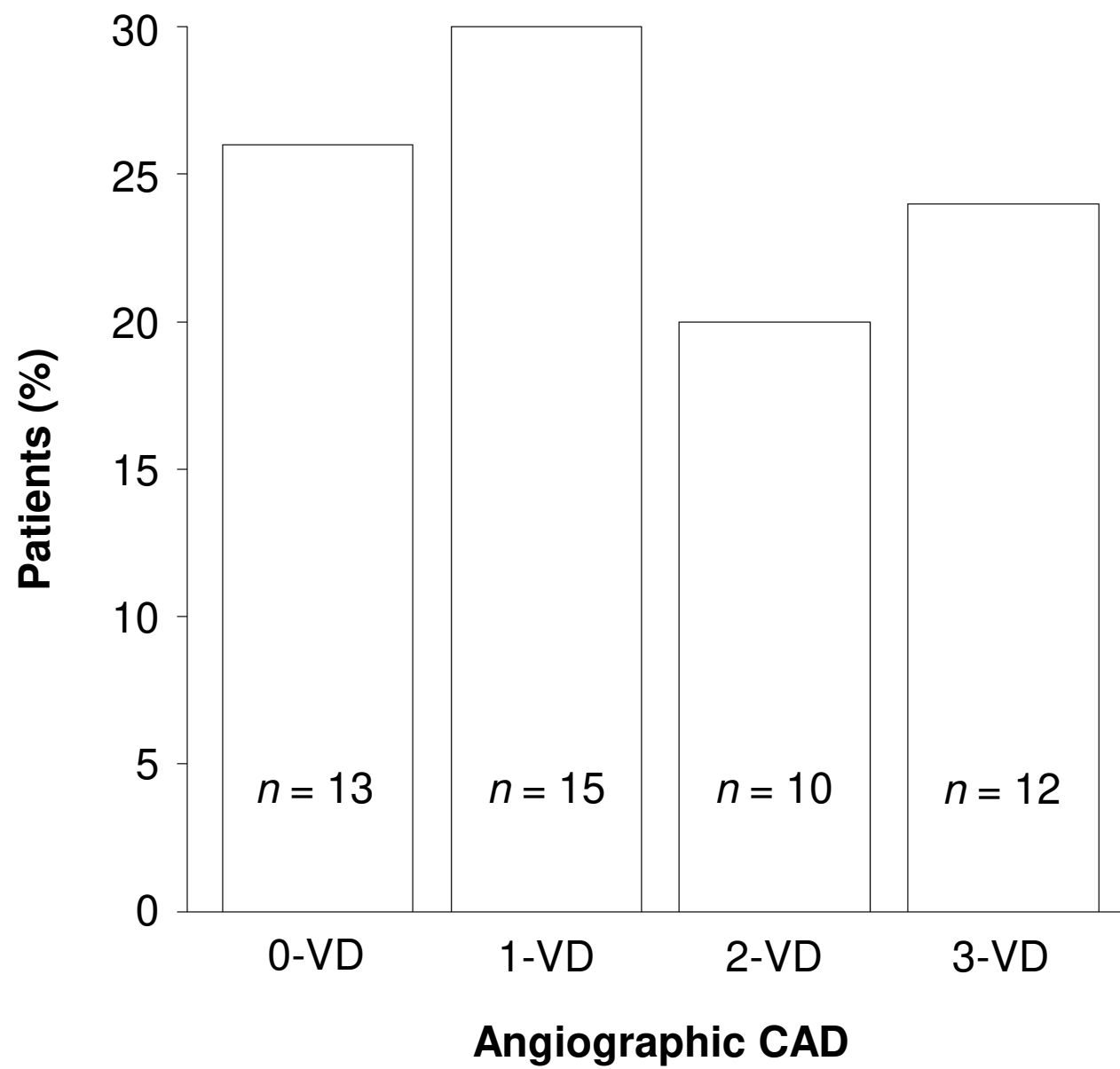


Figure 2

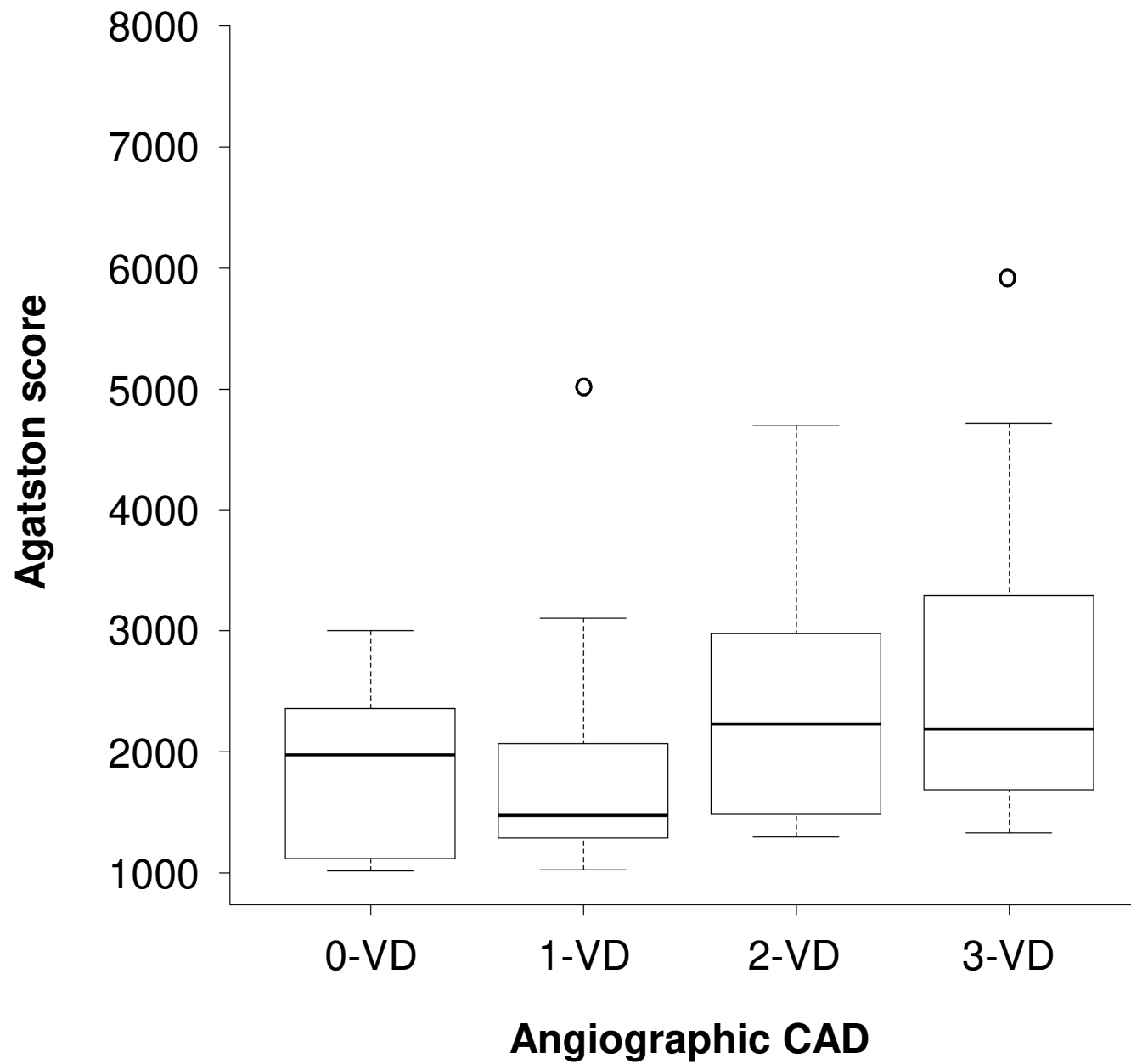


Figure 3